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Metaphyseal Peg in Geroderma Osteodysplasticum: A New Genetic Bone Marker and a Specific Finding?

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We describe two sibs with geroderma osteodysplasticum (GO) who, in addition to the known clinical and radiologic manifestations of the disorder, presented a metaphyseal peg indenting the epiphysis of the long bones, particularly at the knees. The peg was visible only at the age of 4 to 5 years but was invisible in infancy and following physeal closure. This may explain why this anomaly was not described in previous reports of 23 patients in 11 families with GO. The metaphyseal peg is an abnormality of bone development so far unknown to us. We speculate that it represents a primary, age-dependent alteration of bone shape and hence a new genetic bone marker apparently specific to GO. © 1996 Wiley-Liss, Inc.

KEY WORDS: geroderma osteodysplasticum, Bamatter syndrome, metaphyseal peg

INTRODUCTION

Geroderma osteodysplasticum (MIM No. 231070) is a rare autosomal recessive disorder characterized by lax, wrinkled skin, aged appearance, joint laxity, and osteoporosis. The pathogenesis is not known at present [McKusick, 1994; Toriello, 1990]. Radiographic findings consist of generalized osteoporosis, vertebral compression fractures, and long bone fractures. In new born and older infants excessive skin folds can be recognized. Hip dislocations, biconcave vertebral bodies, wormian bones, short stature, malar hypoplasia, and mandibular prognathism have been reported in some cases [McKusick, 1994; Toriello, 1990].

We reviewed the radiographic findings in two sibs with GO. In addition to the known manifestations of GO we found a peculiar peg like extension of the metaphysis into the epiphysis of the long bones. To our knowledge this finding has not been described before. It represents a hitherto unrecognized behavior of the growth plate and possibly a specific finding in GO.

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Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

CLINICAL REPORT

M.R. Female (Patient 1)

Her history was published previously by Suter et al. [1982]. She was born to non-consanguineous healthy parents from the same Italian village. Born at term her weight was 2.23 kg (−2.4 SD) and length was 43 cm (−3.6 SD). Dislocation of both hips at birth, wrinkly skin, right inguinal hernia, hyperextensible joints, calcaneo-valgus and -varus deformity of feet, and multiple spontaneous fractures led to the diagnosis of GO. Her height at 15 years measured 134.7 cm (−4.8 SD). Her proportions and mental development were normal. Results of routine laboratory tests and special studies such as chromosomal analysis, urinary amino acids, mucopolysaccharides, and proteoglycan galactosyltransferase I activity were normal. Electron microscopy of skin showed collagen fibrils of normal, round diameter tightly packed into regular fibers and a reduced amount of elastic fibers. Collagens I, III, and V produced by cultured skin fibroblasts were normal in amount and structure.

V.R. Male (Patient 2)

The brother of patient 1 was born at 37 weeks of gestation, weight was 2.37 kg, and length was 47 cm (both 10th centile). His clinical appearance was similar to that of his sister (Fig. 1): a large fontanelle, wide sutures, bluish sclerae, wrinkly lax skin, hyperextensible joints, decreased abduction of hips, valgus deformity of both feet, and bilateral inguinal hernias were found. Dislocation of hips was noted at birth (Fig. 2). The anterior fontanelle measured 2 × 2 cm at 23 months. At 4 9/12 years mental development was normal and he had proportionate short stature with a height of 95.4 cm (−3.5 SD).

Radiographic Findings

Osteopenia. Moderate to severe osteopenia with thinning of the cortices (particularly in infancy and preschool age) of the tubular bones and decreased bone

Fig. 1. Patient 2 at 3 weeks. Note wrinkled skin, sagging cheeks.

Fig. 3. Patient 2 at 4 3/12 years. Note diffuse osteopenia, and a cone-shaped epiphysis at the distal phalanx of the thumb.

density was present in both patients (Fig. 3). Additionally, there was marked but partially reversible flattening of the thoracic and lumbar vertebral bodies which appeared wedge-shaped and biconcave on lateral view. Sclerotic lines were noted paralleling the endplates of the vertebral bodies (Fig. 4). Mild scoliosis convex to the right and reversible kyphosis of the thoracic spine was seen in patient 1. No evidence for spinal stenosis was present. Multiple fractures of the limbs of both patients were documented beginning at age of 3 months.

Wormian bones. Multiple wormian bones were noted within the lambdoid sutures, and to a lesser degree within the sagittal and coronal sutures in both patients (Fig. 5). Thinning of the cranial vault was seen in infancy.

Dislocation of the hips. Bilateral dislocation was documented on arthrography in patient 1 and ultrasound in patient 2. The hips in patient 2 were reducible and treated with a harness in infancy. Patient 1 underwent open reduction of both hips with varus osteotomies of the femora at age of 7 years. Flattening of the proximal femoral epiphyses was noted in both patients at age 15 years (patient 1) and 4 3/12 years (patient 2), respec-

Fig. 2. Patient 2 at 3 days. Hips are dislocated.

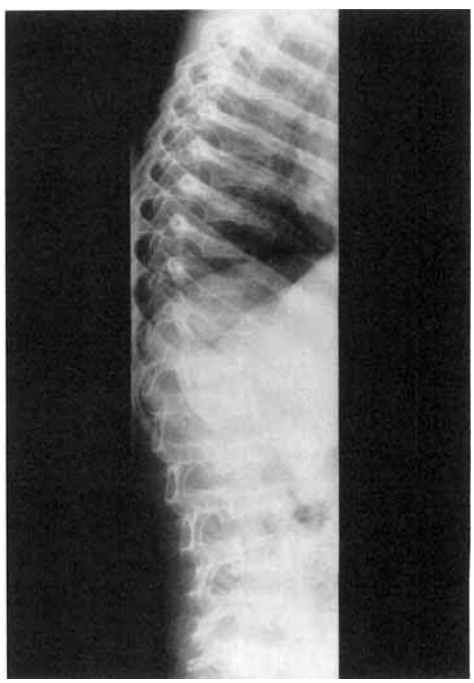

Fig. 4. Patient 2 at 4 3/12 years. There is diffuse osteopenia and generalized platyspondyly of the thoracic and lumbar spine associated with kyphosis. The vertebral bodies appear wedge shaped and biconcave.

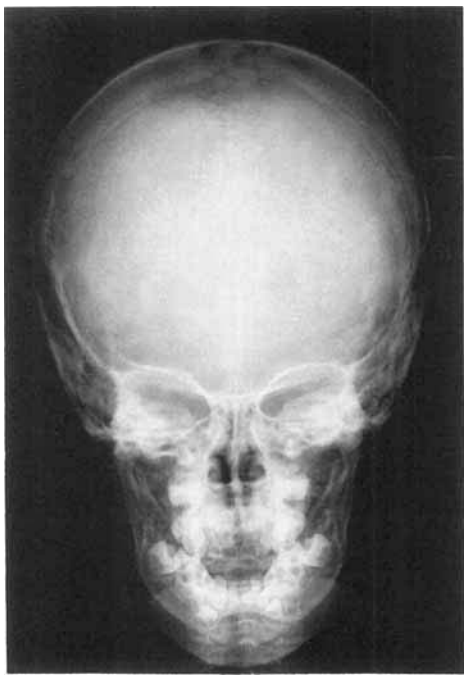

Fig. 5. Patient 2 at 4 3/12 years. Note multiple wormian bones at lambdoid and sagittal sutures, and thin cranial vault.

tively. There was residual subluxation of the left hip in patient 2.

Metaphyseal peg. The knees of both patients appeared normal in infancy without evidence for epi- or metaphyseal dysplasia. By 4 3/12 years (patient 2) and 5 1/2 years (patient 1) a peculiar oval-shaped extension of the metaphysis into an otherwise normal epiphysis was present in the distal femur and proximal tibia bilaterally (Figs. 6A, 7). Similar but less prominent findings were discernible in the proximal humerus (Fig. 6B) and distal tibia (Fig. 6C), but not in the proximal femur (Fig. 6D). MRI examination of the left knee in patient 2 showed an intact, but centrally irregular physis surrounding the metaphyseal extension. The signal intensity of bone marrow and growth cartilage was normal (Fig. 8). Follow-up radiographs of the knees in patient 1 at 15 years after physeal closure showed no residues of the former derangement, particularly no evidence for premature closure of the growth plate (Fig. 9).

Additional radiographic findings. Brachymesophalangy V of the right hand in patient 1 and a relatively large and cone shaped epiphysis of the distal phalanx of the right thumb in patient 2 (Fig. 3) was noted. Apart from osteopenia the hands appeared unremarkable with normal bone age. There was extension of molar roots beyond the inferior dental canal in patient 1; otherwise no abnormality of the teeth was noted, especially no evidence of dentinogenesis imperfecta.

DISCUSSION

GO was first described by Bamatter et al. [1950] in five members of a Swiss family. Later reports based on the same family [Boreux, 1969; Brocher et al., 1968; Demottaz, 1977; Klein et al., 1968] and additional reports from other kinships [Biering et al., 1955; Bonioli et al., 1990; Hunter, 1978, 1988; Lisker et al., 1979; Lustmann et al., 1993; Orazi et al., 1993; Sakati et al., 1983; Suter et al., 1982] (total of 23 patients in 11 families, including patient 1 of our report) emphasized the clinical manifestations of the disorder and the relatively nonspecific radiologic findings of osteopenia, increased number of wormian bones, and the secondary changes of dislocation of the hips associated with small proximal femoral epiphyses, deformity of the feet, platyspondyly, and increased rate of fractures. The limbs were reported to be otherwise unremarkable. Recorded craniofacial abnormalities include malar hypoplasia with relative mandibular prognathism, an enlarged funnel-shaped mandibular lingula, extension of the mandibular premolar and molar roots below the inferior dental canal, and hypercementosis surrounded by a radiolucent halo of several teeth [Brocher et al., 1968; Hunter 1978, 1988; Lisker et al., 1979; Lustmann et al., 1993].

Radiographs of the knees were published in four cases [Brocher et al., 1968; Orazi et al., 1993; Sakati et al., 1983]: in two 16-month-old boys, a 6-year-old boy, and a 16-year-old boy. Physeal irregularities of the distal femora were described in two of the four cases: the 16-month and 6-year-old boys [Orazi et al., 1993; Sakati et al., 1983], but no mention of the metaphyseal peg as described above was made.

Our two patients did not show evidence of an epi- or meta-physeal abnormality in the neonatal and infantile period up to 1 year 6 months. The peg at the knee was discernible only at 4 and 5 years, respectively, but had become invisible at 15 years in patient 1. Therefore it seems to represent an age-dependent finding that appears during early childhood and becomes invisible following physeal closure. It can be missed, if examination of the knees is not performed at the appropriate period, and on superficial inspection it might appear as a mere "irregularity." The relatively subtle peg of the proximal humerus and distal tibia can easily be overlooked.

Small epiphyseal pegs extending into the metaphyses are known to be a normal occurrence in humans and animals. They occur as small projections into the metaphysis and are thought to represent a biologic response to physiologic forces such as shearing and rotational stresses [Ogden, 1990]. More conspicuous extensions into the metaphysis are called cone-shaped epiphyses. They may represent a primary abnormality of growth in certain genetic bone disorders [Giedion, 1967] or an acquired abnormality secondary to premature focal physeal closure as in osteomyelitis and trauma.

The metaphyseal peg extending into the epiphysis at the knees, shoulders, and ankle joints as observed in our two patients to our knowledge is a previously undescribed finding. An equivalent projection from the midportion of the metaphysis without indentation of the epiphysis of only the distal phalanges of the digits was seen in children with untreated primary hypothyroidism [Hernandez et al., 1979].

The pathogenesis of the metaphyseal peg is not clear. We speculate that it more likely represents a primary abnormality of bone growth and formation than

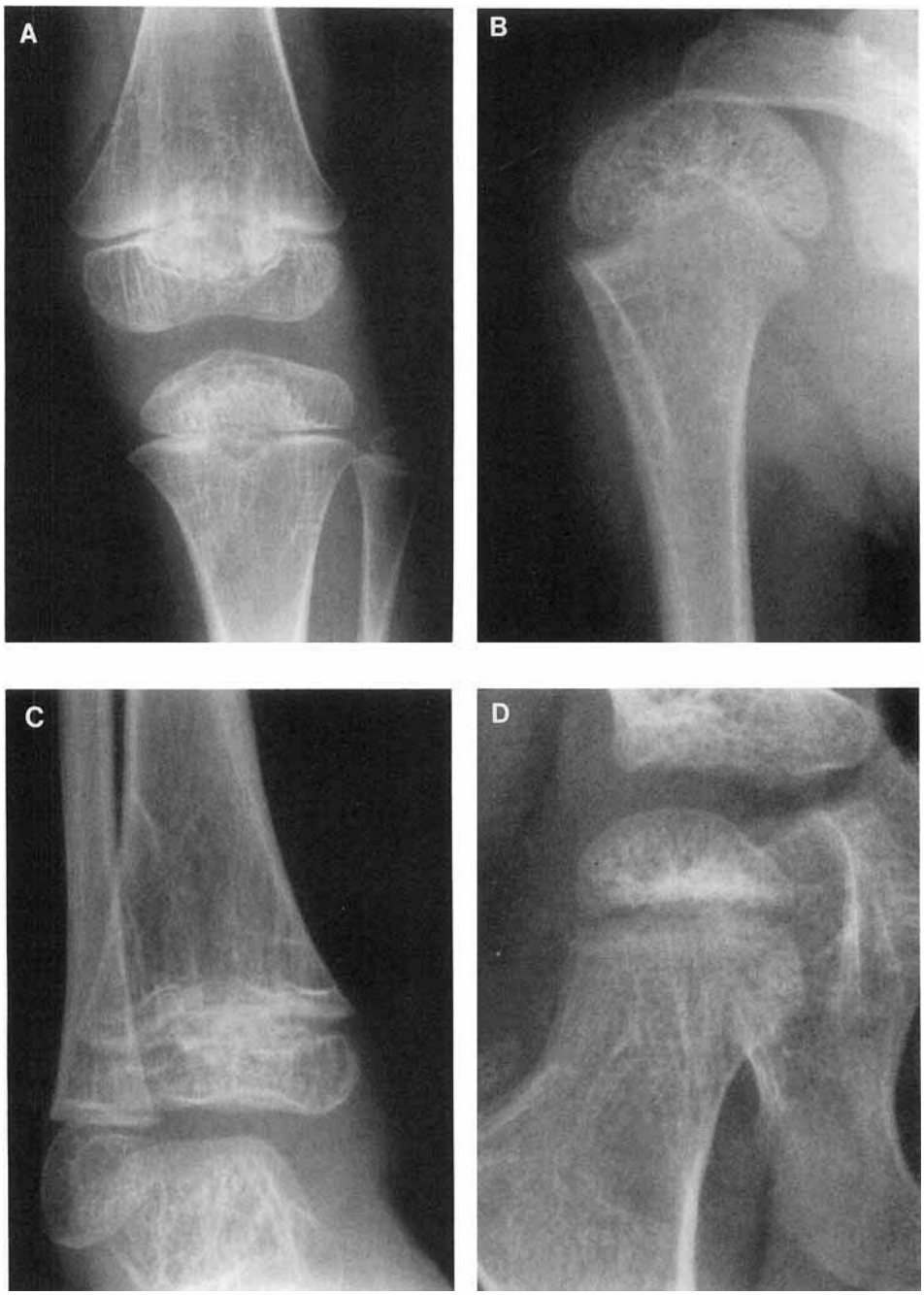

Fig. 6. Patient 2 at 4 3/12 years. **A:** Note peg like central extension of the metaphysis into an otherwise normal epiphysis of the distal femur and proximal tibia. **B:** A less marked metaphyseal peg is noted in the proximal humerus. **C:** The central portion of the distal tibial physis appears sclerotic and irregular due to a small metaphyseal peg. **D:** The proximal femoral epiphysis is diminished in height and diameter, but no distinct peg is noted.

a secondary abnormality related to osteopenia, since other disorders with osteopenia, such as osteogenesis imperfecta, do not exhibit this trait. Therefore the metaphyseal peg may belong to the group of primary alterations of bone shape as seen in genetic bone diseases. Like other bone markers [Giedion, 1994] the peg is age dependent and might have been missed in previous descriptions of GO because of lack of imaging the appropriate region at the appropriate time, and because the peg can be misinterpreted as a simple physeal irregularity, particularly in the shoulder and ankle joint region.

Fig. 7. Patient 1 at 5½ years. Similar metaphyseal pegs of distal femur and proximal tibia to patient 2.

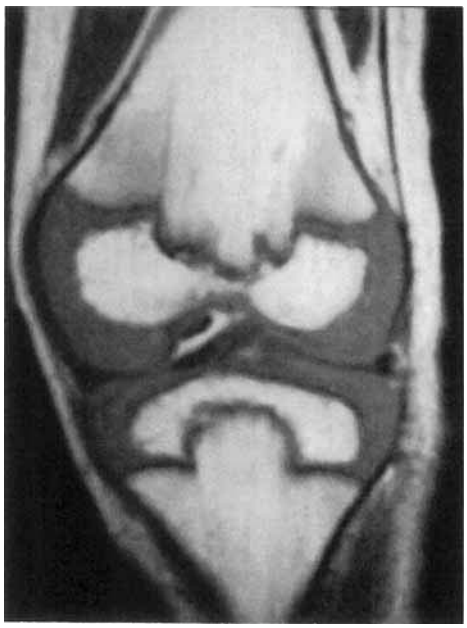

Fig. 8. Patient 2 at 4 4/12 years. MRI (T1-weighted) in coronal plane of left knee showing central extension of metaphysis into the epiphysis of distal femur and proximal tibia. Note irregular but intact physis and normal marrow signal intensity.

Fig. 9. Patient 1 at 15 3/12 years. Following physeal closure no residue of the metaphyseal peg is noted.

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REFERENCES

Bamatter F, Franceschetti A, Klein D, Sierro A (1950): Gérodermie ostéodysplasique héréditaire. Ann Paediatr 174:126–127.

Biering A, Iversen T (1995): Osteogenesis imperfecta associated with Ehlers-Danlos syndrome. Acta Pediatr 44:279–286.

Bonioli E, Pinelli G, Di Stefano A, Costa M, Palmieri A, Coviello DA, Bellini C (1990): Geroderma osteodisplastico. Prima segnalazione italiana. Riv Ital Pediatr 16:577–579.

Boreux G (1969): La gérodermie ostéodysplasique à hérédité liée au sexe, nouvelle entité clinique et génétique. J Genet Hum 17: 137–138.

Brocher JEW, Klein D, Bamatter F, Franceschetti A, Boreux G (1968): Röntgenologische Befunde bei Geroderma osteodysplastica hereditaria. Fortschr Röntgenstr 109:185–198.

Demottaz JD (1977): Orthopädische Aspekte bei Geroderma osteodysplastica hereditaria. Orthopade 6:35–38.

Giedion A (1967): Cone-shaped epiphyses of the hands and their diagnostic value. The tricho-rhino-phalangeal syndrome. Ann Radiol 10:322–329.

Giedion A (1994): The weight of the fourth dimension for the diagnosis of genetic bone disease. Pediatr Radiol 24:387–391.

Hernandez RJ, Poznanski AK (1979): Distinctive appearance of the distal phalanges in children with primary hypothyroidism. Radiology 132:83–84.

Hunter AGW, Martsolf JT, Baker CG, Reed MH (1978): Geroderma osteodysplastica: A report of two affected families. Hum Genet 40: 311–324.

Hunter AGW (1988): Is geroderma osteodysplastica underdiagnosed? J Med Genet 25:854–857.

Klein D, Bamatter F, Franceschetti A, Boreux G, Brocher JEW, Holenstein P (1968): Une affection liée au sexe: La gérodermie os-

téodysplasique héréditaire (20 ans d'observation). Rev Oto-Neuro Ophthal 40:415–421.

Lisker R, Hernández A, Martínez-Lavin M, Mutchinick O, Armas C, Reyes P, Robles-Gil J (1979): Gerodermia osteodysplastica hereditaria: Report of three affected brothers and literature review. Am J Med Genet 3:389–395.

Lustmann J, Nahlieli O, Harary D, Casap N, Neder A, Zlotogora J (1993): Gerodermia osteodysplastica: report on two patients and surgical correction of facial deformity. Am J Med Genet 47: 261–267.

McKusick VA (1994): Geroderma osteodysplastica. In: "Mendelian Inheritance in Man: A Catalog of Human and Genetic Disorders." Baltimore and London; The Johns Hopkins University Press, pp. 1846–1847.

Ogden JA (1990): Anatomy and physiology of skeletal development. In: Ogden JA (ed): Skeletal injury in the Child. Philadelphia; W.B. Saunders Company, pp 23–63.

Orazi C, Bartuli A, Barbuti D, Bosman C, Dionisi Vici C, May EH, Sabetta G (1993): Geroderma osteodisplastico o sindrome di Bamatter: Segnalazione di due casi in cugini di primo grado. Riv Ital Pediatr 19:98–103.

Sakati NO, Nyhan WL (1983): Congenital cutis laxa and osteoporosis. Am J Dis Child 137:452–454.

Suter H, Tönz O, Schärli A (1982): Geroderma osteodysplastica hereditaria (GOH) in a girl. Prog Clin Biol Res 104:327–329.

Toriello HV (1990): Osteodysplastica geroderma, Bamatter type. In: Buyse ML (ed): "Birth Defects Encyclopedia." Dover; Center For Birth Defects Information Services, Inc., pp 1316–1318.